REMARKS

Claims 1-9 and 14-27 are in this application. Claims 1, 2, 8 and 9 have been amended. Claims 14-27 have been added.

Claim 1 has been amended to include the SEQ ID NO: 7. A revised sequence listing will be submitted.

Claim 2 has been amended to include Markush language.

Claim 7 has been amended to delete the extra "]".

Claim 8 has been amended to define a composition comprising a polypeptide according to claim 1 and a pharmaceutically acceptable carrier. Claims 14-19 defining pharmaceutically compositions comprising the peptides of claims 2-7 respectively have been added. Support for these claims is found, inter alia, on page 1, line 8, page 4, lines 15-17 and in original claim 8.

Support for claims 20-27 is found, inter alia, in Examples 6 and 7 and original claim 9.

The Examiner has rejected claims 1-9 under 35 USC 112, first paragraph. Applicants respectfully traverse this rejection.

Claims 1-7 of this application are claims to peptide derivatives. The Examiner's rejection refers to pharmaceutical compositions and methods of treatment. There is no basis for a rejection of claims 1-7 under 35 USC 112, first paragraph. The Examiner states that the application includes a description of how to make the peptides of claims 1-7, their use *in vitro* to determine cytotoxic effect or activity of the peptides in various human cell lines and *in vivo* antitumor activity on PTC xenograft in nude mice. Therefore, since claims 1-7 are clearly enabled, it is respectfully requested that the rejection of claims 1-7 under 35 USC 112, first paragraph be withdrawn.

The rejection of claims 8 and 9 under 35 USC 112, first paragraph must also be withdrawn.

Claim 8 has been amended to define a composition comprising a peptide derivative according to claim 1 and a pharmaceutically acceptable carrier. This is supported as explained above. This claim and new claims are enabled as one of ordinary skill in the art given the teachings of this application of the peptide derivatives and the knowledge of preparation of pharmaceutical compositions would be able to prepare and use the claimed compositions.

Claim 9 has been amended and claims 20-27 have been added.

As regards the examiner's contention that no working example or

data or evidence is provided which shows that the claimed peptides individually are useful as a pharmaceutical composition by administering as an effective ingredient a therapeutically effective amount of the peptide to treat cancer in mammals, the examiner's attention is drawn to Example No 7, wherein a method and dose of treating cancer with SEQ ID : 3, in mice has been described. The peptide composition comprises the peptide solubilized in water. Alternately, the peptide may be solubilized in any of the other solvents commonly used. The example describes administering a total dose of 25.2 ug/day. One of skill in the art is aware that the actual dosage of a drug administered to a patient depends on a number of factors including the age, sex, condition, general health, etc. of the patient.

The Examiner is requested to consider the following additional evidence which is pertinent to pharmaceutical compositions of the peptides, including the dosage amount and protocols of using a therapeutically effective pharmaceutical composition for treating cancer in general.

Example

Pharmaceutical composition and therapeutic dose of claimed peptides

An example within the scope of the invention comprises use of peptides SEQ ID NO : 2 to SEQ ID NO : 6. The molar concentration of each of the peptides where it is expected to be active ranges from 10^{-6} M to 10^{-9} M. However, it is expected that these peptides would be effective if the concentration of each ranged from approximately 10^{-5} M to approximately 10^{-10} M or even higher or lower.

A formulation of each of these peptides for *in vitro* use may be prepared in the following way. A stock solution of each of the peptide analogs is prepared with a pH of approximately 7.0 to approximately 7.4. Although sterile phosphate buffered saline was used to prepare the stock solutions for the testing described below, other diluents may be used such as RPMI 1640, buffered saline, isotonic NaCl, Ringer's solution, water (for injection), distilled water, polyethylene glycol (neat or in water), 2% Tween in water, dimethylsulfoxide to 50% in water, propylene glycol (neat or in water), balanced salt solution, glycerol, and other conventional fluids that are suitable for intravenous administration. To obtain a pH in the range of approximately 7.0 to 7.4 for each stock solution, the pH can be adjusted by using 1N HCL for lowering the pH or 1N NaOH for raising the pH, although other conventional agents for adjusting the pH can be used. The concentration of the peptide analog is approximately 10^{-3} M. This is further diluted using the above-mentioned diluents to give a final concentration of 10^{-8} M. In one exemplary embodiment, the pH of the peptide solution may range from approximately 7.0 to approximately 7.4. To obtain a pH in this range, the pH can be adjusted by using 1N HCl for lowering the pH or 1N NaOH for raising the pH, although other conventional agents for adjusting the pH can be used.

The methods of this invention comprise, consist of, or consist essentially of: administering systemically to the mammal a therapeutically effective quantity of any of the mentioned peptides SEQ ID NO : 2 to SEQ ID NO : 6. An effective dose ranges form 10 to 200 ug (preferably 50 to 150 ug) of the peptides per kg of the body weight of the mammal, with the dose dependent on the effects sought, the manner of administration, the peptides selected, and the cancer being treated. Systemic administration refers to oral, rectal, nasal, transdermal, and parental (i.e., intramuscular, intravenous and subcutaneous). In accordance with good clinical practice, it is preferred to administer the composition at a dose that will produce anticancer effects without causing undue harmful side effects. The composition may be administered either alone or as a mixture with other therapeutic agents.

The composition may optionally and preferably contain pharmaceutically acceptable diluents, excepients, solvents, binders, stabilizers, and the like. Such diluents may include: RPMI 1649, buffered saline, isotonic NaCl, Ringer's solution, water, distilled water, polyethylene glycol (neat or in water), 2% Tween in water, dimethylsulfoxide to 50% in water, propylene glycol (neat or in water), phosphate buffered saline, balanced salt solution, glycerol, and other conventional fluids that are suitable for intravenous administration. Pharmaceutical composition which provide from about 0.1 to 10.0 mg of the composition per unit dose are preferred and are conventionally prepared as tablets, lozenges, capsules, powders, aqueous or oily suspension, syrups, elixirs, and aqueous solutions. The nature of the pharmaceutical composition employed will, of course, depend on the desired route of administration.

In regard to claim 9, it is noted that the compounds have been tested on sufficiently large number of cell lines. It may be noted that SEQ IDs 2-6 were tested on 7 human tumor cell lines representing breast, glioblastoma, lung, oral cavity, larynx, ovary and endothelial cancers.

In the opinion of the inventors, the compounds have been tested on sufficiently large number of cancers, which include cancers of different types such as adenocarcinoma, squamous cell carcinoma, cancer of the central nervous system and endothelioma. Since all the tested compounds show cytotoxic activity on all the cell lines tested, it is reasonable to believe that these compounds would show anticancer activity on other adenocarcinomas (such as cancers of the gastrointestinal tract, prostate, renal, hepatic, bladder, oesophagus, etc), squamous cell cancers (head and neck, skin, non small cell lung cancer, etc), cancers of central nervous system (neuroblastomas, astrocytomas, meduloblastomas, etc) and endotheliomas.

Extrapolation from in vitro results to in vivo results is consistent with standard protocols used in the art. Attached is a copy of the article "The National Cancer Institute: Cancer Drug Discovery and Development Program", Seminars in Oncology, Vol. 19. No. 6, 1992: pp. 622-638. In this article in the last paragraph in the second column on page 626 it is explained that in 1985

the National Cancer Institute made the decision to use human tumor cell lines in an *in vitro* assay as the primary cancer screen. On the next page it is explained that leads identified using this model can be examined further by *in vivo* models. It is explained in the first column on page 630 that agents that have positive results in *in vitro* screens are then tested in an animal using human tumor xenografts. "Those agents that show significant growth inhibition or tumor regression will be selected for further *in vivo* evaluation against more advanced staged tumors." See in addition MPEP 2107.03 which states that data from in vitro testing is generally sufficient to support therapeutic utility.

Therefore, it is respectfully requested that this rejection be withdrawn.

The Examiner has rejected claims 1-9 under 35 USC 112, second paragraph. Applicants respectfully traverse this rejection.

The Examiner states that claims 1-9 is indefinite because it does not recite the function, activity or use of the peptide of the formula referred to in claim 1. There is no requirement that a claim to a peptide which is essentially a chemical include a function, activity or use. 35 USC 101 provides for the patentability of a composition of matter. Peptides are compositions of matter. US patents claiming peptides and chemical compounds are routinely granted and such claims do not include the function, activity or use of a claimed peptide or compound. See for example, US Patents 6,420,380; 6,441,130; 6,441,131; 6,441,132 and 6,451,968. The function and use of the peptides is described in the specification. Therefore, it is respectfully requested that this rejection be withdrawn.

Page 6 of the specification has been amended to include "reverse phase C18 column" after LICHROCART® C_{18} and C_{18} LICHROSPHER®, WP-300.

Accordingly, applicants submit the present application is in condition for allowance and favorable consideration is respectfully requested.

Respectfully submitted,

Janet I. Cord
c/o Ladas & Parry
26 West 61st Street
New York, NY 10023
Reg. No. 33,778
(212) 708-1935

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In the Specification

Please replace page 3, paragraph 3 with the following:

-- The present invention relates to peptides of the following general formula

X-Leu-Met-Tyr-Pro-Thr-Tyr-Leu-Lys-Y (SEQ ID NO:7)

wherein,

X is acetyl or straight, branched, or cyclic alkanoyl group of from 3-16 carbon atoms. –

Please replace the second full paragraph on page 6 with the following:

-- The resulting crude peptide was purified by preperative high performance liquid chromatography (HPLC) using a [LiChrOCART®] LICHROCART® C_{18} (250. Times. 10) (reverse phase C-18 column)) reverse phase column (Merck, Darmstadt, Germany) on a Preparative HPLC system (Shimadzu Corporation, Japan) using a gradient of 0.1% TFA in acetonitrile and water. The eluted fractions were reanalyzed on Analytical HPLC system (Shimadzu Corporation, Japan) using a C_{18} [LiChrospher®] LICHROSPHER®, WP-300 (300 X 4) (reverse phase C-18 column) reverse-phase column. Acetonitrile was evaporated and the fractions were lyophilized to obtain the pure peptide. The identity of each peptide was confirmed by electron-spray mass spectroscopy. –

In the Claims

Claim 1. (amended) A peptide derivative of the formula

X-Leu-Met-Tyr-Pro-Thr-Tyr-Leu-Lys-Y (SEQ ID NO:7)

wherein, X is acetyl or straight, branched, or cyclic alkanoyl group from 3-16 carbon atoms and

Y is carboxy terminal residue selected from OH or amino; or a pharmaceutical acceptable salt of the peptide.

Claim 2. (amended) A peptide derivative of claim 1, wherein the alkanoyl [groups] group is selected from the group consisting of acetyl, n-butanoyl, n-hexanoyl, n-octanoyl, lauroyl, myristoyl, palmitoyl, isohexanoyl, cyclohexanoyl, cyclopentylcarbonyl, n-heptanoyl, n-decanoyl, n-undecanoyl, [or] and 3,7-dimethyloctanoyl.

Claim 7. (amended) A peptide derivative of claim 1, wherein X is Palmitoyl

and the peptide is:

Palmitoyl-Leu-Met-Tyr-Pro-Thr-Tyr-Leu-Lys-OH (SEQ ID NO:6) [ ]]

or a pharmaceutically acceptable salt thereof.

Claim 8. (amended) A composition comprising [an effective amount of] a polypeptide according to claim 1, and a pharmaceutically acceptable carrier.

Claim 9. (amended) A method of treatment of cancer in mammals which comprises the administration of a [an effective amount of] polypeptide according to claim 1, alone or in combination with other polypeptides or anticancer compounds <u>in an amount effective to treat with cancer</u>.